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14. ABSTRACT

A randomized, double-blinded, placebo-controlled clinical trial was conducted to evaluate the effectiveness of propranolol, topiramate, and amitriptyline as treatments for chronic post-traumatic headaches secondary to combat-related mild head injury. The study has completed the third of three years. 305 soldiers with chronic PTH were screened and 64 were enrolled, falling well short of the enrollment target of 240 subjects. 39 (61%) had evaluable data after drug titration and 34 (53%) completed the 3-month treatment period. Discontinuation rates ranged from 39% for topiramate to 53% for amitriptyline but were not significantly different between treatment arms. Monthly headache days decreased from 12.2 at baseline to 7.9 during the final month in all subjects (-36%, p=0.0001), 16.7 to 8.7 in the placebo arm (-48%, p=0.012), 11.7 to 6.1 in the amitriptyline arm (-41%, p=0.0005), 14.0 to 8.3 in the propranolol arm (-41%, p=0.10), and 9.3 to 8.8 in the topiramate arm (-5%, p=0.80). Mean MIDAS scores decreased from 71 at baseline to 31 at the final visit among all subjects (p=0.0001) and significantly declined in the placebo, topiramate, and propranolol arms. PTSD symptom checklist scores significantly declined in the topiramate arm. This study is limited by the small number of subjects and better than expected response in the placebo arm. The study is closed.

15. SUBJECT TERMS

Headache, mild head trauma, concussion, treatment, clinical trial

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Introduction

Headaches are the most common symptom after mild traumatic brain injury (1-4). Chronic post-traumatic headaches (PTHAs) develop in 20% of TBI victims, contributing to disability, healthcare utilization, and poor quality of life (5-6). There are no prospective, controlled clinical trials evaluating medical treatments for chronic post-traumatic headaches (7).

The purpose of this study was to determine the effectiveness of propranolol, amitriptyline, and topiramate as treatments for chronic PTHAs. We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, multi-arm trial to evaluate propranolol, amitriptyline, and topiramate for treatment of chronic PTHAs. The enrollment target was 240 patients meeting International Classification of Headache Disorders (ICHD) diagnostic criteria for chronic post-traumatic headaches. Subjects were recruited from the Traumatic Brain Injury Program and the Neurology Clinic at Madigan Army Medical Center, Ft. Lewis, WA. Study participants were U.S. Army soldiers with chronic post-traumatic headaches attributable to mild traumatic head injury sustained while deployed to a combat theater. Participants were randomized to receive placebo, propranolol 80 mg daily dose, amitriptyline 50 mg daily dose, or topiramate 100 mg daily dose for 3 months. The primary outcome measure was the number of moderate-severe headache days during the third month of treatment. Secondary outcome measures included the proportion of subjects with at least a 50% reduction in headache frequency, headache-related disability as measured by the Headache Impact Test and Migraine Disability Assessment Scale, PTSD symptom checklist score, and medication tolerability. The findings of this study will improve the care of patients with chronic headaches after traumatic brain injury.

Body:

Over the 3-year study period, 305 soldiers were screened for study enrollment and 64 were enrolled. Of these, 39 (61%) had evaluable data after drug titration and 34 (53%) completed the 3-month treatment period. Discontinuation rates ranged from 39% for topiramate to 53% for amitriptyline but were not significantly different between treatment arms. The most commonly identified reason for a subject discontinuing the study was that he moved away from the geographic region. No serious adverse events occurred.

Monthly headache days decreased from 12.2 at baseline to 7.9 during the final month in all subjects (-36%, p=0.0001), 16.7 to 8.7 in the placebo arm (-48%, p=0.012), 11.7 to 6.1 in the amitriptyline arm (-

41%, p=0.0005), 14.0 to 8.3 in the propranolol arm (-41%, p=0.10), and 9.3 to 8.8 in the topiramate arm (-5%, p=0.80). ≥50% responder rates were 49% (19/39) for all subjects, 50% (3/6) for placebo, 67% (8/12) for amitriptyline, 44% (4/9) for propranolol, and 33% (4/12) for topiramate. Mean MIDAS scores decreased from 71 at baseline to 31 at the final visit among all subjects (p=0.0001) and significantly declined in the placebo, topiramate, and propranolol arms. HIT-6 scores and PTSD symptom checklist scores significantly declined in the topiramate arm only.

Key Research Accomplishments:

1. 18 subjects were enrolled in the last year. A total of 64 subjects were enrolled in the study over 3 years. The study is now closed to enrollment.
2. Follow-up of all enrolled study subjects has been completed.
3. A study database has been completed.
4. Data analysis was performed.
5. An abstract reporting the study findings was submitted to the American Academy of Neurology.

Reportable Outcomes:

1. An abstract of the study findings has been submitted for presentation at the 2012 American Academy of Neurology meeting in April, 2012.

2. Erickson JC, Neely E, Theeler BJ. Post-traumatic Headache. *Continuum: Lifelong Learning in Neurology*. December, 2010; Vol 16(6):55-78.

Conclusion:

This study is limited by the small number of subjects and the unexpectedly high responsiveness of the placebo arm. Amitriptyline-, propranolol-, and topiramate were associated with significant improvements in headache frequency and/or headache-related disability though no treatment was superior to placebo. Topiramate was also associated with a significant improvement in PTSD symptoms. The study drugs were similarly tolerated. The slower than expected enrollment rate and the high discontinuation rate (47%) reveal significant challenges in conducting a 4-month study in this population. The findings will be useful for designing large multi-center clinical trials to conclusively evaluate the efficacy of headache prophylactic therapies for chronic PTH in military personnel.

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Supporting Data:

Table 1. Number of subjects in each treatment arm.

Treatment	#Randomized	# completing drug titration	#Completing study
Placebo	12	6 (50%)	6 (50%)
Topiramate	18	12 (67%)	11 (61%)
Propranolol	17	9 (53%)	9 (53%)
Amitriptyline	17	12 (71%)	8 (47%)
All	64	39 (61%)	34 (53%)

Table 2. ≥50% response rates in each treatment arm.

Treatment	Responders (≥50% decrease)
Placebo	3/6 (50%)
Topiramate	4/12 (33%)
Propranolol	4/9 (44%)
Amitriptyline	8/12 (67%)
All	19/39 (49%)

Table 3. Change in monthly headache days.

		Mean Monthly HA days/month (SD)				
Treatment	n	Baseline	Final	Change	% Change	Paired t-test
Placebo	6	16.67	8.67	-8.0	-48%	0.0121
Topiramate	12	9.25*	8.83	-0.42*	-5%	0.80
Propranolol	9	14.0	8.33	-5.67	-41%	0.10
Amitriptyline	12	11.67	6.08	-5.58	-41%	0.0005
All	39	12.23 (6.39)	7.85 (6.21)	-4.38	-36%	0.0001

p=0.01 compared to placebo

Table 4. Headache-related disability as measured by the MIDAS and HIT-6.

	MIDAS			HIT-6		
Treatment	Baseline	Final	paired t	Baseline	Final	paired t
Placebo	83.17	27.83	0.008	63.17	51.33	0.122
Topiramate	62.27	25.00	0.019	61.6	56.5	0.046
Propranolol	68.5	29.13	0.046	64.38	53.5	0.167
Amitriptyline	75.0	45.86	0.21	55.7	52.0	0.32
All (n=32)	70.53(47.8)	31.13(38.28)	0.0001	61.29(5.92)	53.71(13.62)	0.0034

Table 5. Depression symptoms (PHQ-9) and PTSD symptoms (PCL).

	PHQ-9			PCL		
Treatment	Baseline	Final	paired t	Baseline	Final	paired t
Placebo	13.17	10.5	0.39	49.0	45.8	0.63
Topiramate	11.45	9.82	0.55	48.1	38.3	0.0495
Propranolol	10.0	8.75	0.32	42.3	37.1	0.40
Amitriptyline	8.29	8.00	0.87	37.7	36.1	0.66
All (n=32)	10.72(4.84)	9.28(7.06)	0.21	44.2 (16.21)	38.9 (17.75)	0.047

Appendices: none